Tubulointerstitial Diseases

Introduction

These diseases are nephron diseases but not of the glomerulus. That means they are neither nephritic nor nephrotic. They have nothing to do with red blood cells, dysmorphic red blood cells, or a kidney biopsy. You will see these diseases in clinical practice far more often than any of the glomerular diseases in the lessons that follow.
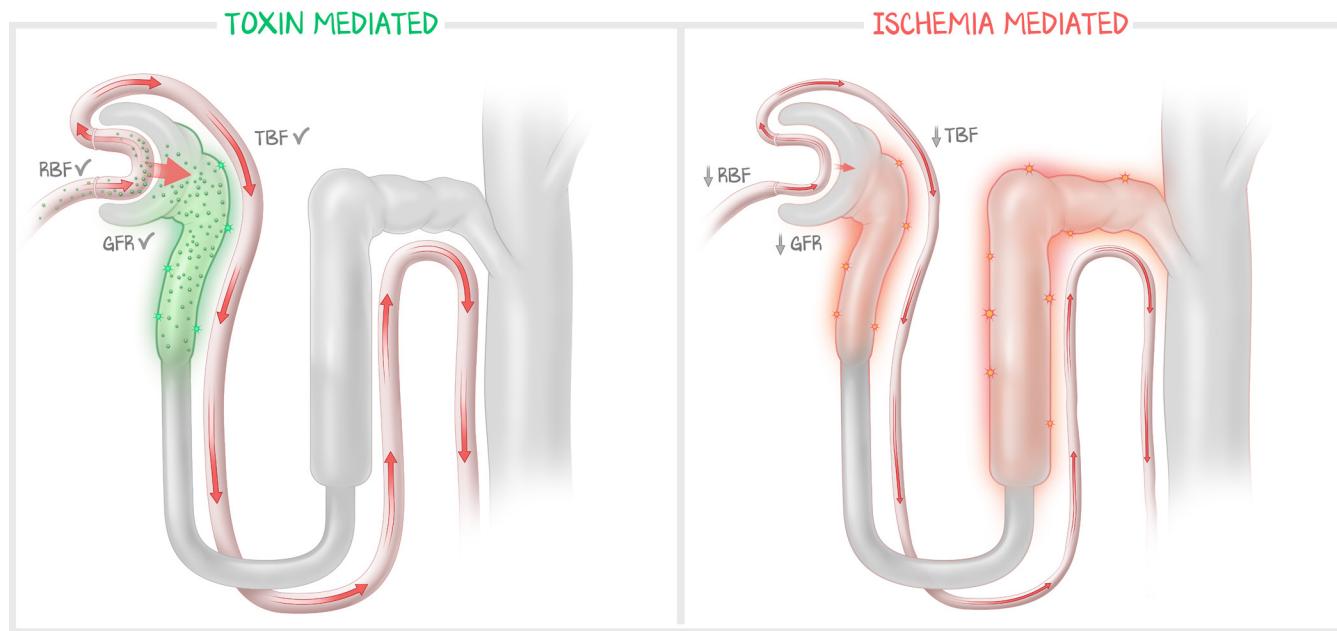
There is a lot to know about acute tubular necrosis and acute interstitial nephritis. Acute tubular necrosis is caused by either ischemia of tubule cells or exposure of the tubule cells to filtered toxins. It progresses in three phases. You must be able to identify the phases and communicate both the filtration forces and the renal blood flow at each phase. Acute interstitial nephritis has three causes, three distinct presentations that you should learn as separate diseases. You must be able to spot them, anticipate the urine findings, and know the causative agents behind them. We also sprinkle in renal papillary necrosis and cortical necrosis.

Acute Tubular Necrosis/Acute Tubular Injury

The term acute tubular necrosis, and even more so its abbreviation, ATN, have been firmly established in both scientific descriptions and medical vernacular. But because the result is not always necrosis (the pattern of neutrophils, macrophages, and fibroblasts is not seen), an attempt to transition to "acute tubular injury," or ATI, is being made in pathology texts. Since you are going to hear "ATN" and "AKI" (acute tubular necrosis is a cause of acute kidney injury), we are not going to mention ATI again. It is too close to commonly used abbreviations that it would be dangerous for your learning.

The epithelial lining of the tubules is responsible for **reabsorption**. Some segments of the tubule have it easier than others. The passive diffusion of water that occurs in the concentrating segments of the descending loop of Henle requires no ATP. The cells still need oxygen to survive, but they don't have a metabolic demand like the other segments. Those segments that actively reabsorb ions rely on the sodium gradient established by the **Na⁺/K⁺-ATPase** on their basolateral membrane. These cells have a massive oxygen demand. **Ischemia affects these segments the most** (thick ascending limb of the loop of Henle and the distal convoluted tubule). The collecting duct is also impacted, but not to the same extent.

The proximal convoluted tubule was excluded from the discussion in the previous paragraph. Because the PCT is the first segment to receive literally everything filtered by the nephron, it has the toughest job of all. The PCT is where the vast majority of absorption occurs. For the same reason as the DCT and TAL, the **PCT is vulnerable to ischemia**. But the PCT is vulnerable for another reason. Any toxin filtered by the glomerulus is exposed to the epithelial cells of the PCT first. The PCT receives the highest dose of toxin, and therefore ATN caused by exposure to toxins affects the PCT most.
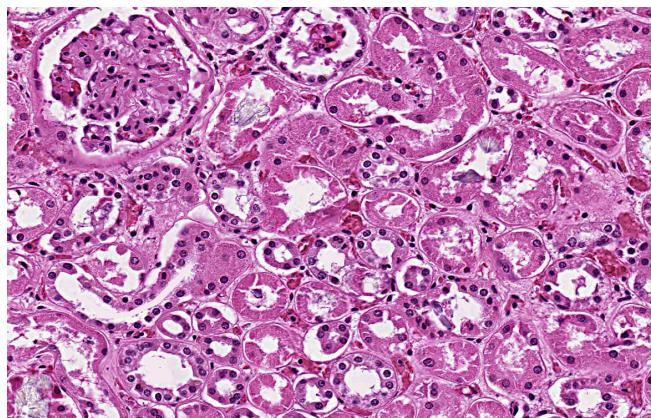
Figure 2.1: Acute Tubular Necrosis Mechanisms
The proximal convoluted tubule receives the highest dose of toxin and so is the most affected by toxin-induced acute tubule necrosis. The segments with active Na$^+$/K$^+$-ATPases, the diluting segments, have high metabolic demands. These areas are at risk of ischemia-induced acute tubular necrosis. The segments that reabsorb water do so passively. The descending limb is the least affected in all conditions.
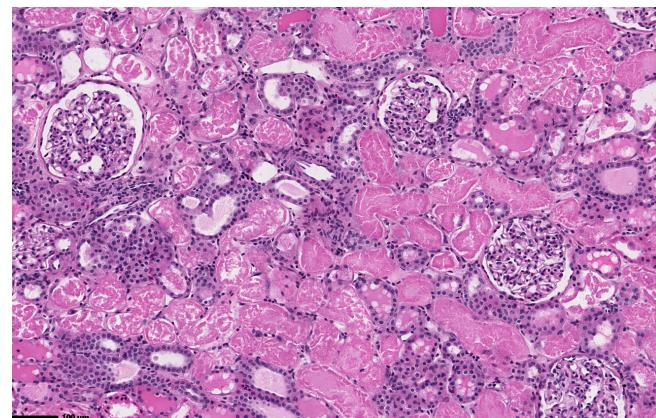
ATN, therefore, occurs as a result of either severe ischemia or toxic exposure. **Severe ischemia** may be from a prolonged prerenal azotemia (not severe reduction in flow, but made to feel severe because of how long a nonsevere reduction lasted) or from an acute sudden loss of perfusion (as occurs in shock kidney). **Toxic exposure** is classically manifested by exposure to **radiocontrast dye** (a creatinine of 1.5 mg/dL or greater is a contraindication to intravenous contrast), **amphotericin B**, **myoglobin** (as seen in rhabdomyolysis), **aminoglycoside** antibiotics (the most common drug to cause ATN), **heavy metals** (such as the drug cisplatin or severe lead poisoning), and **uric acid** (as seen in tumor lysis syndrome). That may seem like just a list to memorize and have no logical links. For now, that will have to do. Radiocontrast, myoglobin, and aminoglycosides have a much higher prevalence in clinical practice.

Ischemia rarely results in necrosis. Instead, the loss of ATP increases cytoplasmic calcium load (by not being able to remove the calcium from the cytoplasm despite reabsorbing it) which activates caspases—**apoptosis**. If a biopsy is performed (you shouldn't need to do one, and should make the diagnosis based on history) you would see **absent nuclei** in the cells lining the tubules. Ischemia and apoptosis induce the loss of cell-to-cell junctions, especially the **zona occludens** which normally informs the epithelium that it is intact. This causes a loss of polarity as the epithelial cells come apart from one another. This loss of polarity is visualized by the **loss of the brush border** on the normal absorptive apical surface. Finally, epithelial cells **detach from the basement membrane** and accumulate in the tubular lumen, forming casts. Infiltration of the tissue by leukocytes is NOT seen.

(a)

(b)
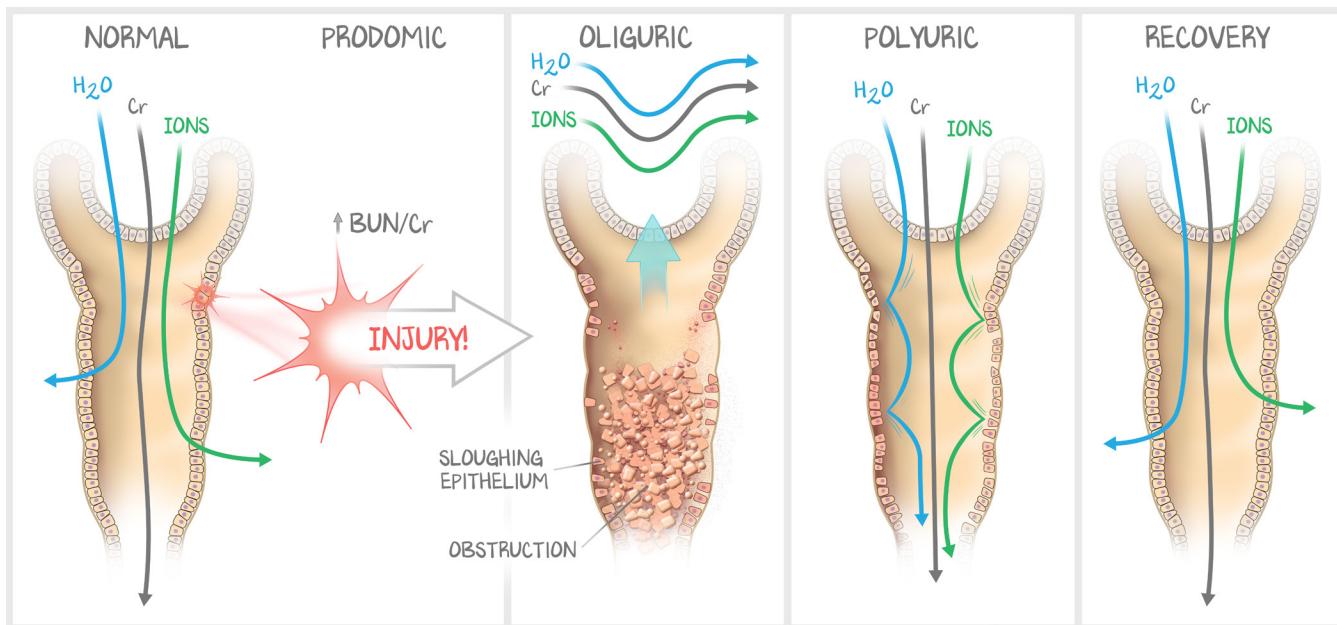
Figure 2.2: Acute Tubular Necrosis
(a) The circles of pink without the blue dots are necrotic—the cells missing their nuclei undergoing coagulative necrosis, esepcially visible at 6 o'clock and 4 o'clock. (b) Severe necrosis. Multiple normal glomeruli are scrattered throughout the field. The pools of nuclei (dark dots) between glomeruli and tubules are leukocytes which have invaded the tissue. The pink junk is the epithelial casts formed in what should be tubules (they should be white).

When the cells slough off into the tubules, they smush together, **conforming to the shape of the tubule**. This will be seen as **waxy brown casts** in the urine. But the casts accumulating within the tubules results in a miniature obstructive picture—every glomerulus feels an obstruction of its own tubule's lumen. This backpressure from Bowman's space reduces GFR, worsening levels of BUN and creatinine. Worse, with impaired GFR the macula densa senses reduced flow and activates RAAS, reducing blood flow to the tubules, exacerbating the injury.
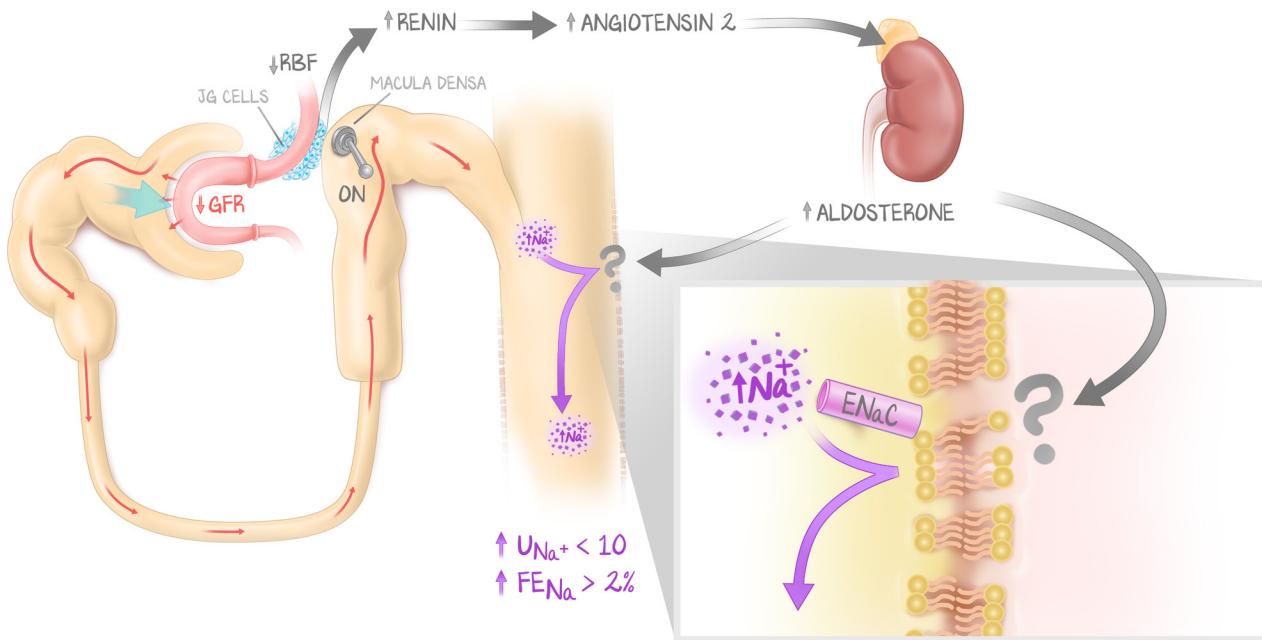
If a patient enters **ATN** for any reason, there will be a **predictable sequence**. The **initiation phase** is a short period where the nephrotoxic insult has occurred, but renal failure has not set in yet. The BUN and Cr start to rise. The **oliguric phase** (also called maintenance phase) results in **little to no urine output**. The GFR falls to near zero, fluid is retained, and electrolyte dysregulation (**especially hyperkalemia**) occurs. Without management, the patient dies. With **dialysis**, **supportive care**, and **time**, the kidneys often recover. The tubule cells are stable cells. They slough off, form casts, and are expelled, causing renal failure. But the epithelium is capable of regenerating. Regenerating takes time and no further insult. Before the tubule epithelial cells recover, the casts of the old cells are washed away, alleviating the back pressure on the glomerular capillaries. Filtration recovers. But because the tubule epithelial cells have not fully recovered, while **filtration recovers**, **reabsorption does not**. Normal function with impaired reabsorption results in a **polyuric phase** (also known as the recovery phase), in which a massive diuresis occurs. This diuresis may cause **hypokalemia** and will **intravascularly deplete** the patient. In the oliguric phase, IV fluids would have only drowned the patient. Now in the polyuric phase, vigorous IV fluid replacement and electrolyte supplementation is required to keep up with the diuresis. As the epithelium recovers, reabsorption recovers, and normal homeostasis is achieved.

Figure 2.3: Acute Tubular Necrosis Phases
In the normal condition, water, creatinine, and ions are filtered. Water and ions are reabsorbed. Filtration and reabsorption are normal. Tubule injury happens, and the prodromal phase starts. As the tubule cells slough off into the lumen, they form an obstruction and the hydrostatic forces from Bowman's space prevent filtration of creatinine, water, and ions. Reabsorption would be impaired, but because filtration is impaired so severely there is so little to reabsorb. Therefore, low filtration of water means lower urine volumes (thus oliguria). Low filtration of creatinine means elevated creatinine. As the casts clear but the epithelium is not fully recovered, filtration becomes unimpaired. Reabsorption remains impaired. The normal filtration occurs but excess urine volumes and excess urine electrolytes deplete the patient of both. As the epithelium returns, reabsorption is restored, and both filtration and reabsorption are normal.

Because the tubules are damaged, they are unable to reabsorb what is filtered. An **increased distal sodium** load results in a $\mathbf{FE_{Na} > 2\%}$. BUN cannot be reabsorbed, so the **BUN:Cr ratio is < 10**. These tests are not meaningful the way they are for prerenal azotemia, but some texts still insist on comparing them. The FE_{Na} itself is not a great test. In truth, the only time the FE_{Na} is useful is when the person had normal kidneys and now is oliguric. To go from totally normal to so deranged they are in renal failure generally has an obvious cause. Using the FE_{Na} to figure out if it is prerenal or intrarenal seems quite ridiculous.

Figure 2.4: Sodium Reabsorption in ATN
Not all filtration stops. What little filtration there is includes water and sodium. With poor GFR there is poor flow through the nephron. The tenin-angiotensin-aldosterone axis is activated. Aldosterone attempts to reabsorb sodium. The tubules are damaged, so no sodium is reabsorbed. Sodium is lost to the urine. Therefore, the fractional excretion, the amount filtered that ends up in urine, is high. The amount of sodium is low because the amount filtered is low (because GFR is low). But the percentage reabsorbed is reduced, so the percentage lost, the fractional excretion, is increased.

Cortical Necrosis
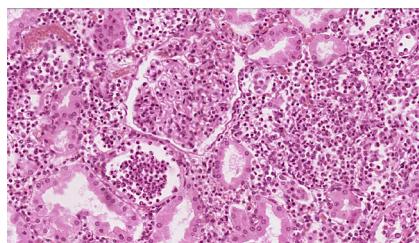
True cortical **necrosis** can occur. This would be from massive interruption in blood flow, akin to disseminated intravascular coagulation or severe hypotension. The blood vessels enter the hilum, travel up the renal columns, with the most distal arteries, the arcuate arteries, penetrating the cortex. In periods of severe, prolonged hypotension, the tissue with the most distal vascular supply undergoes the worst ischemia. Ischemia in the kidneys results in a **coagulative necrosis**. This will be seen across the entire cortex, every glomerulus, PCT, and DCT affected.

Acute Interstitial Nephritis
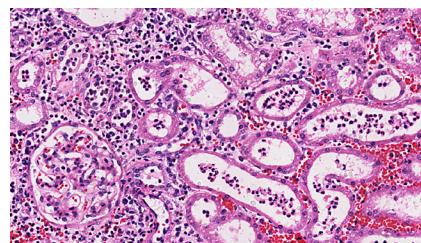
This is an -itis of the interstitium. This means that when you look at the biopsy (you shouldn't biopsy AIN; you should be able to figure it out clinically) you will see **many blue cells in the interstitium** and maybe in the tubules. Those dark blue or purple nuclei are leukocytes. Which leukocyte is present is determined by which of the three AIN variants is currently at play—infectious (aka pyelonephritis), allergic, or analgesic.

The first is **infectious**, in the form of **pyelonephritis**, where organisms have gained access to the tubules by ascending the ureters. This necessitates first that the patient had bacteria in her bladder (a cystitis). Patients will complain of urgency, frequency, and dysuria. In addition, because pyelonephritis ascends the tubules, it causes inflammation of the renal cortex and capsule, resulting in **costovertebral angle tenderness**. There is usually severe toxicity, with elevated temperature and white blood cell count. The neutrophils fighting the bacteria often spill into the urine, forming **white blood cell casts** visible in the urine. There is no eosinophilia in acute infectious pyelonephritis.
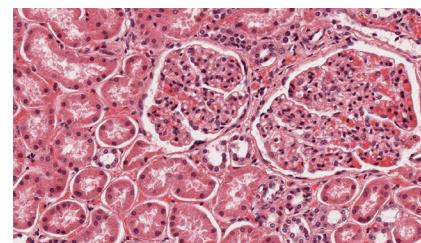
The second is **allergic**. There are many ways this can occur. But we use the word "allergic" to remind you that this form of AIN presents with **eosinophils**. Eosinophils in the urine is indicative of AIN. This form of AIN stems from **medications**, mostly, and those that are associated with allergic reactions in general are the usual culprits. **Penicillins** and **cephalosporins** in particular, antibiotics used to treat pyelonephritis, can worsen renal function with this inflammatory allergic reaction. **TMP/SMX**, another antibiotic used to treat UTIs (albeit rarely used for this purpose), can do it, too. The commonality between these antibiotics? Sulfur. **Diuretics**, which are used in an attempt to treat overload (which, if given in excess could cause prerenal azotemia, a condition that is NOT interstitial nephritis), can cause the allergic reaction, too. There are many others. We want you to remember only, "sulfur antibiotics used to treat UTIs" and "diuretics used to treat volume overload," so we aren't telling you the others. On the test, look for **fever**, **peripheral eosinophilia**, **urine eosinophils**, and a **rash** (reticular and may be full body) that starts several days into a treatment course with antibiotics.


(a)   **(b)**   **(c)**

Figure 2.5: Acute Interstitial Nephritis
(a) Acute pyelonephritis. Many neutrophils between ducts and forming a cast within the duct next to the glomerulus.
(b) Acute interstitial nephritis. Many eosinophils fill the spaces between the ducts and can be seen in the ducts on the right of the image. At this power, you can detect the red hue to the eosinophils not present in the neutrophils. (c) Normal. The only purple dots (nuclei) are in the cells that line the duct lumen, ducts are very close together without any intervening cell/nuclei.

The third is **analgesic related**. Aspirin and NSAIDs reduce prostaglandins, induce vasoconstriction, and result in papillary necrosis (**pyramids suffer**). The interstitial nephritis follows. If caught in the early phases, the patchy papillary necrosis is reversible. If it is allowed to be prolonged, here will be total papillary necrosis (the entire pyramids die) resulting in frank hematuria. Necrosis leads to inflammation, which can result in **fibrosis**. Volume depletion and AKI for other reasons, combined with NSAIDs, exacerbate this form of interstitial nephritis. Papillary necrosis is not unique to analgesic interstitial nephritis, and can be seen in sickle cell disease and diabetes. However, chronic NSAIDs, hematuria, and urine eosinophils should alert you to the diagnosis of analgesic nephropathy.

Usually with treatment of the infection, removal of the allergic drug, and removal of the analgesic, the kidney can recover with supportive care. Remove the source of inflammation, then give the kidney time. The more scarring that occurs, the worse the resultant baseline renal function. But you can't see that clinically; that would be on biopsy alone. Instead, you will wait for their creatinine to level off and their rash to go away to determine the course.

DISEASE	CHARACTER
Acute Tubular Necrosis	ATN is caused by **ischemia**—shock kidney, prolonged prerenal azotemia • Ischemia causes diffuse patchy tubular necrosis in any segment (low flow everywhere) ATN is caused by **toxins**—myoglobin, contrast dye, cisplatin, aminoglycosides • Toxins cause focal PCT necrosis Look for **muddy brown casts** in the urine With death of tubules, unable to reabsorb sodium = ↑Na excretion = **> 2% FE$_{Na}$** Three phases: **Evolution** (slight ↑BUN), **Oliguric** (GFR = 0, ↑K, HD) → **Polyuric** (Volume and electroyte repletion)
Acute Interstitial Nephritis: Allergic Nephritis	Administration of drug does nothing until **concentrated in tubules**, leading to immunogenicity **Eosinophils** in the urine, blood, and biopsy slide Allergic nephritis will see a **fever**, **reticular rash**, and **eosinophils** with ↑**Cr** Commonly caused by **penicillins**, **cephalosporins**, and **diuretics**
Acute Interstitial Nephritis: Analgesic Nephropathy	**NSAIDs** ↓Prostaglandins, resulting in vasoconstriction Causes **papillary necrosis** Look for **chronic pain** (a reason to take pain meds) **Phenacetin** (in acetaminophen preparations) has been tested. Acetaminophen itself is hepatotoxic. Increases risk for **transitional cell carcinoma** of the renal pelvis
Acute Interstitial Nephritis: Pyelonephritis	Is technically an AIN, caused by bacteria ascending through the ureters Tubules have **bacteria** in them, and **macrophages**/**neutrophils** enter to fight infection Spills over into the interstitium **White blood cell casts** in urine Fever, flank pain, dysuria, urgency, frequency. Discussed in more detail in the UTI lesson.

Table 2.1: Tubulointerstitial Diseases